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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/732,163	Applicant(s) WARBURTON ET AL.	
	Examiner Brian Whiteman	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Interview Summary on 11/30/01* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *2 and 8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7 and 9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☑ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5 .
4) ☒ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Priority

Priority to application no. 60/169,545 filed on 12/7/99 is acknowledged.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-2 and 4-12, drawn to a method of stimulating the growth of lung alveolar surface in a lung comprising: providing cells capable of regenerating lung alveolar surface; and administering cells to lung, wherein the lung is in vivo, classifiable in class 424, subclass 93.1

II. Claims 1 and 3-7, 9-12, drawn to a method of stimulating the growth of lung alveolar surface in a lung comprising: providing cells capable of regenerating lung alveolar surface; and administering cells to lung, wherein the lung is ex vivo, classifiable in class 424, subclass 93.1.

Claim 1 link(s) inventions I and II. The restriction requirement between the linked inventions is subject to the non-allowance of the linking claim(s), claim 1. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or non-statutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable.

See *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Although there are no provisions under the section for "Relationship of Inventions" in MPEP 806.05 for inventive groups that are directed to different methods, restriction is deemed to be proper because each of the methods of inventions I and II constitutes patentably distinct inventions for the following reasons: Each of the inventions is directed to different goals and comprises materially distinct steps, wherein each of the compositions in each invention is structurally distinct and/or generates distinct mechanisms and functional effects as indicated above. The scope of each of the cited inventions encompasses an employed method, which generates distinct function(s) and effect(s), and furthermore does not necessarily overlap with that of another invention. Furthermore, none of the method steps cited in inventions II recite a similar method of administering cells to lung that is in vivo as encompassed in Group I. Each of the inventions I and II comprises materially distinct steps, and/or generates different functions and effects, and thus, is not required for use with one another. Therefore the invention of groups I and II are distinct.

Because these inventions are distinct for the reasons given above and the search required for Group I is not required for Group II, restriction for examination purposes as indicated is proper.

It would be unduly burdensome for the examiner to search and consider patentability of all of the presently pending claims, a restriction for examination purposes as indicated is proper.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 § 1.17(h).

During a telephone conversation with Mr. Ken Sibley on November 30, 2001, a provisional election was made without traverse to prosecute the invention of Group II, claims 1, 3-7, and 9-12. Affirmation of this election must be made by applicant in replying to this office action.

Claims 2 and 8 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 6.

Specification

The specification contains misspelling of the word "homologous" on page 10, line 15. These and any other, spelling errors should be corrected in response to this office action. Applicant is encouraged to review the specification for additional spelling errors.

Claims 1, 3-7, and 9-12 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-7, and 9-12, as best understood, are readable on a genus of a progenitor or stem cells capable of regenerating lung alveolar surface, wherein the genus of progenitors or stem cells are not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates that a species of stem/progenitor cells exist in the distal lung and can regenerate both alveolar epithelium and capillaries (page 9). Furthermore, the specification contemplates that exogenous stem cells for use in administering to subjects are either created by nuclear transfer of the recipients own genetic material into embryonic stem cells, or collected from either autologous bone marrow, lung biopsy, or from endobronchial lavage (page 9).

However, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of progenitor or stem cells that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient to support the present claimed invention directed to a genus of progenitor or stem cells capable of regenerating lung alveolar surface. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming unspecified progenitor and/or stem that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus progenitor or stem cells that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 1, 3-7, and 9-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled

in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possession of a genus of progenitor or stem cells capable of regenerating lung alveolar surface), particularly in view of the reasons set forth above, one skilled in the art would not have known how to use and make the claimed invention so that it would operate as intended, e.g. regenerating lung alveolar surface.

The field of the invention encompasses a method of stimulating the growth of lung alveolar surface in a lung of a mammal in need of such treatment comprising: providing progenitor or stem cells capable of regenerating lung alveolar surface; and administering said cells to said lung (complete or a fraction of a lung) in an amount sufficient to stimulate the growth of the lung alveolar surface, wherein the lung is ex vivo and then transplanting said lung into the mammal.

The state of the art for tissue restoration displays that cell transplants have been used in several areas, (Stocum et al., Wound Rep Reg, Vol. 6, pp. 276-290, 1998). Stocum teaches that over the past 50 years, we have made progress in our ability to replace body parts with devices,

solid organs, and tissue transplants, or both (page 277). Such replacement parts, however, still pose significant biological problems, and they are not useful for all situations (page 277). Furthermore, Stocum teaches that providing reliable sources of cells for cell transplant is crucial issue that requires establishing culture banks or proliferating stem, progenitor, or differentiated cells that can be drawn on as required, as well as cell culture media that support the proliferation and differentiation of these cells (page 284).

Furthermore, the state of the art for stem cell therapy as exemplified by Richter et al., (Int. J. Hematol, Vol. 73, pp. 162-169, 2001), teaches that

> Hematopoietic stem cells (HSCs) have been considered particularly important as target cells because of their pluripotency and ability to reconstitute hematopoiesis after myeloablation and transplantation. Genetic correction of HSCs can therefore potentially last a lifetime and treat hematologic disorders in which genetic deficiencies cause the pathology. Retroviral vectors have been the main vectors to transduce human HSCs because of their ability to integrate into the chromosome of their target cells. Gene transfer efficiency of murine HSCs is high using retroviral vectors. In contrast, gene transfer using the same viral vectors to transduce human HSCs or HSCs from large animals has been much lower. Although these difficulties may have several causes, the main reasons for the low efficiency of human HSC transduction with retroviral vectors is because of the non-dividing nature of HSCs. Murine HSCs can be easily stimulated to divide in culture, whereas it is more problematic to stimulate human HSCs to divide rapidly in vitro. Because retroviral vectors require dividing target cells for successful

nuclear import of the preintegration complex and subsequence integration of the provirus, only the dividing fraction of the target cells can be transduced.

Furthermore with respect to lung transplantation, the state of the art for lung transplantation has gained widespread acceptance as a therapeutic option for a diverse array of lung diseases as taught by Arcasov et al. (Medical Progress, Vol. 340, pages 1081-1091. Nonetheless, complications are frequent and result constraints on long-term preservation of graft function and patient survival (page 1081). The common complications are primary graft failure, airway complications, infection, acute rejection, and chronic rejection (pages 1087-1088). Lung transplantation ha reaches its current clinical plateau largely through refinements in the selection of patients, operative techniques, and postoperative care (page 1088). Two major hurdles must be overcome to increase the applicability of lung transplantation and improve long-term results: the supply of donor organs must be increased to meet the demand, and chronic rejection must be more effectively prevented (page 1088).

In addition, with respect to lung stem cells, the state of the art as exemplified by Magdaleno et al., (Adv Pediatr, Vol. 45, pp. 363-96, 1998), Magdaleno teaches that before stem cells can used for therapeutic purposes understanding tissue genetics and immunology is essential (pages 363-364). Animal models or repair provide some clues about which cells are the stem cells in the lung (page 373). However, this approach is complex and oftentimes it is difficult to identify the specific molecular events that govern lung cell gene expression (page 373). In the course of studying the evidence for specific stem cells in the lung, one consensus perpetually emerges: the processes of lung development, gene regulation, and injury repair are multi-step processes involving a concerted effort between extracellular and intracellular input to

elicit proliferation and/or differentiation of specific epithelial cell types of the airways (page 388).

The disclosure provides working examples: Example 1 (pages 10-16) displays that exogenous fibroblast growth factor 10 (fgf10) can stimulate wild type lung morphogenesis and rescues cells that were exposed to nitrogen in an in vitro cultures of murine lung cells. Example 2 (pages 16-22) encompasses hyperoxia treatment of adult rat and fetal rat alveolar epithelial type 2 cells (AEC2) isolated in cell cultures. The results from example 2 show that telomerase activity is observed in rat fetal AEC2 and can be re-induced in adult AEC 2 following hyperoxic injury. Furthermore, the disclosure contemplates a method of inducing lung regeneration by autologous stem cell replacement, wherein the stem cells are genetically modified (pages 9-10).

The as-filed specification provides sufficient guidance for one skilled in the art to use exogenous fgf10 to stimulate growth in an in vitro culture of murine lungs cells. However, the as-filed specification fails to provide sufficient guidance in several critical areas which encompass: 1) how to make and/or use any progenitor or stem cells in the method of the claimed invention, 2) how to determine what progenitor or stem cells are capable of regenerating lung alveolar surface, 3) how to remove a lung or portion thereof, 4) how to administer said cells to said lung or portion thereof, 5) what amount is sufficient to stimulate the growth of lung alveolar surface, 6) how to avoid a graft vs. host response in a mammal, and 7) how to transplant a lung into any mammal. The as-filed specification fails to provide sufficient guidance for how stimulating murine lung cells in vitro can reasonably correlate to any method for treating any mammal that needs growth of the lung alveolar surface using progenitor or stem cells in an ex vivo method of cell therapy. In view of the art of record, which teaches, "drawing analogies

from the studies performed in rodents to human lung development raises certain caveats, however, because lung development in humans differs from that observed in rodents, See pages L1197-L1198 (Applicants' own work, Driscoll et al., Am J Physiol Lung Cell Mol Physiol, Vol. 279, pp. 1191-98, 2000)." Furthermore, Driscoll teaches that, "the data presented in the disclosure raises question to whether telomerase expression in the repairing lung is simply a marker for proliferation and whether it is expressed more ubiquitously than would be expected for a stem cell population (page L1196)." In addition, Driscoll teaches that because no method exist at the time the application was filed an currently for following the fate of individual cells in the lung, it is impossible to determine when and how telomerase expression is induced an how long it persists in each individual cell (page L1197)." In view of the art of record and the as-filed specification, it would take one skilled in the art an undue amount of experimentation to reasonably correlate from the disclosure to any ex vivo cell therapy method for stimulating the growth of the lung alveolar surface in any mammalian lung for a therapeutic result and transplanting lung back into a mammal. In view of the concerns stated by the art of record, the as-filed specification does not provide sufficient guidance for one skilled in the art to make and/or use any progenitor or stem cells in any method of stimulating the growth of lung alveolar surface in any mammal's lung. Thus, in view of the In re Wands Factors, the disclosure is not enabled for the claimed invention.

In addition, with respect to claims 1, 3-7, and 9-12, the specification fails to provide what stem cells or progenitor cells are capable of regenerating lung alveolar surface in any mammal. The specification states that, "there are stem cells in the distal portion of the lung that can regenerate alveolar epithelium," however, the disclosure fails to provide sufficient guidance for

what cells are capable of regenerating alveolar epithelium. The as-filed specification contemplates that any growth factor may be used to carry out the claimed invention and cites art of record (page 9), which list several growth factors. However, the art of record does not list what growth factors are required to make the stem cells or progenitor cells into cells that can be used in any method to stimulate the growth of lung alveolar surface. In view of the art of record (Stocum, pages 284-285), one skilled in the art understands that culturing stem cells into specialized cells (e.g. lung alveolar surface cells) would require an undue amount of experimentation in view of the art of record and the disclosure, since neither provides sufficient guidance for what growth factors and culture media is required to culture and support the proliferation and differentiation of any cells into cells that could be used in a method of stimulating the growth of lung alveolar surface.

Furthermore, with respect to using any progenitor or stem cells in any ex vivo method of cell therapy for stimulating the growth of lung alveolar surface, the as-filed specification fails to provide sufficient guidance for what type of progenitor or stem cells are capable of regenerating lung surface and how to circumvent the problem with the mammal's immune system when the mammal is exposed to allogenic, xenogenic, or a genetically modified lung or portion thereof. See Stocum page 285, **Evasion of the immune system** and Arcaso, page 1086-1088, **common complications**.

Furthermore, in view of the breadth of claim 12, the claim reads on stem cells, which are genetically modified and the art of record teaches that large animals or human HSCs are hard to transduce because of the nature of HSCs and the specification lacks sufficient guidance for one skilled in the art to circumvent this concern in order to use stem cells that are transduced with a

vector carrying a therapeutic gene in a method of ex vivo cell therapy of a lung. Furthermore, the specification lacks sufficient guidance for one skilled in the art to reasonably correlate the working examples in the disclosure to any method of treating any genetic lung disorder or disease in any mammal. In addition, the state of art with respect to stem cell gene therapy exemplified by Cavazzana-Calvo et al. (*Bailliere Clinical Haematology*, Vol. 12, pp. 129-138, 1999). Cavazzana-Calvo teaches that:

> In spite of very attractive preliminary results obtained in murine studies, therapeutically efficient gene transfer in human targeted cells must be proven (abstract). Each gene protocol must be adapted according to a number of factors, particularly the source of stem cells, donor age, cytokine combinations and in vivo pre-treatment of patients (page 133). The reciprocal of these factors on the gene transfer efficiency has not been elucidated, and knowledge of these interactions should help to improve future clinical results (page 133).

The disclosure does not provide what transgenes could be used in the method and what amount of transgene expression is required for a therapeutic effect to be observed in any mammal with a genetic disorder or disease. Furthermore, Riddell (*Nature Medicine*, Vol. 2, pp. 216-223, 1996) performed an immunotherapy trial in which individuals seropositive for HIV received CD8+ HIV-specific cytotoxic T cells modified by retroviral transduction to express a gene permitting positive and negative selection (abstract). The subjects developed cytotoxic T-lymphocyte response specific for the novel protein and eliminated the transduced cells (abstract). In addition, Riddell demonstrated the persistence of adoptively transferred autologous CD8+ HIV specific cytotoxic T-cell clones modified to express hygromycin phosphotransferase (hy)

gene and the herpes virus thymidine kinase (TK) gene is limited by the induction of a potent CD8+ class I MHC-restricted CTL response specific for epitopes from derived from the hyTK protein (pg. 217). In conclusion, Riddell discusses that immune responses have not been reported after the infusion of bone marrow derived cells, tumor-infiltrating lymphocytes, polyclonal EBV-reactive CTLs, and polyclonal T cells into which the neo gene were introduced with retroviral vectors (pg. 220). Riddell suggest several possible reasons for these results compared to his experimental data (pg. 220). One point noted by Riddell is that the CD8+ HIV-specific CTLs were administered multiple times and may have enhanced antigen-presenting capabilities (pg. 220). If multiple administration of modified T cells to HIV patient causes the genetically modified T cells to be rejected due to the host immune response; than it is not apparent how the claimed invention circumvents this problem particularly since gene therapy usually requires multiple administrations of the therapeutic gene due to the transient expression of the gene. Thus, the disclosure is not enabled for any method of ex vivo cell therapy for treating any genetic defect or disease in any mammal using genetically modified progenitor or stem cells.

Furthermore, with respect to claim 12, wherein said embryonic stem cells contain a nucleus that is autologous to said subject, the claim reads on using stem cells from the same mammal or stem cells from a different mammal that comprise a cell nucleus that is autologous to said mammal. The disclosure lacks sufficient guidance for one skilled in the art to make genetically cells created by nuclear transfer from one cell to another stem cell. The state of the art for somatic nuclear transfer is considered unpredictable as exemplified by Polejaeva et al. Theriogenology, Vol. 53, pp. 117-126, 2000). This technique suffers from several serious

limitations. The most profound is that DNA can only be added, not deleted, or modified in situ. Also, the integration of foreign DNA is random, which could lead to erratic transgene expression due to the effects at the site of incorporation. In addition, with random integration the possibility exists for the disruption of essential endogenous DNA sequences or activation of cellular oncogenes, both of which would have deleterious effects on the animal's health. Finally, animals generated by using pro-nuclear microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. See page 119. Therefore, the as-filed specification and the art of record do not provide sufficient guidance for one skilled in the art make a stem cell comprising a cell nucleus that is autologous to said mammal. Thus, it would take an undue amount of experimentation to use a somatic nuclear transfer for making a stem cell with a cell nucleus that is autologous to said mammal.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made do not provide reasonable enablement for the claimed invention. In view of the state of the art for lung transplantation, stem cell therapy, wherein the stem cells are used in an ex vivo cell therapy wherein any method is employed to correct a genetic disorder in any mammal was unpredictable at the time the invention was made, the lack of sufficient guidance to any therapeutic method of stem cell therapy, the breadth of the claims, one skilled in the art could not make and/or use the invention without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, 3-7, and 9-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "lung in need thereof" in claim 1 is a relative term, which renders the claim indefinite. The term "lung in need thereof" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The disclosure does not define the metes and bounds of the term. Clarification is requested.

The term "recipient in need thereof" in claim 3 is a relative term, which renders the claim indefinite. The term "recipient in need thereof" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The disclosure does not define the metes and bounds of the term. Clarification is requested.

The statement in claims 3-7 and 9-11, "A **method** according to claim 1," is indefinite because it does not point out which method **a method** is referring to in the claim. The dependent claim should state "**The** method of claim 1".

Claims 4-6 and 12 recite the limitation "subject" pages 23 and 24. There is insufficient antecedent basis for this limitation in the claim.

Claim 6 recites the limitation "step" in line 21, page 23. There is insufficient antecedent basis for this limitation in the claim.

The statement in claim 12, "A **method** according to claim 11," is indefinite because it does not point out which method **a method** is referring to in the claim. The dependent claim should state "**The** method of claim 11."

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ms. Tracey Johnson whose telephone number is (703) 305-2982. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached at (703) 305-4051.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-2742.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-8724.

Brian Whiteman
1633
12/3/01

DAVE T. NGUYEN
PRIMARY EXAMINER